

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1-120. (canceled)

121. (previously presented) A binding partner for a TSH receptor, which binding partner comprises or is derived from

- (a) a human monoclonal antibody reactive with the TSH receptor;
- (b) a human recombinant antibody reactive with the TSH receptor; or
- (c) a fragment of a human monoclonal antibody or a human recombinant antibody reactive with the TSH receptor

wherein the binding partner has a characteristic of patient serum TSH receptor autoantibodies

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

127. (previously presented) The binding partner of claim 126, wherein the binding partner has an inhibitory activity of at least 120 units of International Standard NIBSC 90/672 per mg.

128. (previously presented) The binding partner of claim 121, which has the characteristics of patient serum TSH receptor autoantibodies with respect to stimulation of cAMP production by cells expressing the TSH receptor.

129. (previously presented) The binding partner of claim 128, wherein the binding partner has a stimulatory activity with respect to cAMP production of at least 30 units of International Standard NIBSC 90/672 per mg.

130. (previously presented) The binding partner of claim 129, wherein the binding partner has a stimulatory activity with respect to cAMP production of at least 240 units of International

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

134. (previously presented) The binding partner of claim 121, wherein the binding partner comprises a VH domain as shown in Seq. ID NO: 1, or one or more VH CDRs selected from SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4.

135. (previously presented) The binding partner of claim 134, whercin the binding partner further comprises an antibody VL domain as shown in SEQ ID NO: 6, or one or more VL CDRs selected from SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9.

136. (previously presented) A binding partner according to claim 121, wherein the binding partner is a fragment of a human monoclonal antibody or a human recombinant antibody reactive with the TSH receptor and has an inhibitory activity with respect to TSH binding to the TSH receptor of at least 30 units of International Standard NIBSC 90/672 per mg.

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

wherein the binding partner has a characteristic of patient serum TSH receptor autoantibodies and in combination with TSH has stimulatory activity for the TSH receptor, blocks the stimulatory activity of TSH and the a binding partner for the TSH receptor, according to claim 121, and is thereby capable of rendering the TSH receptor substantially inactive or substantially unresponsive to TSH and TSH receptor autoantibodies.

139. (currently amended) A further binding partner according to claim 138, which when present in an assay to measure the antagonistic properties thereof with respect to blocking the stimulatory activity of the a binding partner for the TSH receptor or TSH according to claim 121, results in a greater than 50% reduction in the stimulatory activity thereof.

140. (canceled)

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

144. (canceled)

145. (previously presented) A further binding partner according to claim 143, which comprises an antibody VH domain as shown in SEQ ID NO. 19, or one or more VH CDRs with an amino acid sequence selected from SEQ ID NO. 20, SEQ ID NO. 21 and SEQ ID NO. 22.

146. (previously presented) A further binding partner according to claim 143, which further comprises an antibody VL domain as shown in SEQ ID NO. 24, or one or more VL CDRs with an amino acid sequence selected from SEQ ID NO. 25, SEQ ID NO. 26 and SEQ ID NO. 27.

147. (withdrawn) A polynucleotide comprising a region encoding an antibody VH domain, VL domain or CDR as shown in any one of SEQ ID NOS: 10-13, 15-18, 29-32 or 34-37, wherein the region

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

34-37, wherein the fragment is a Fab fragment, a Fd fragments, a Fv fragment, a dAB fragment, an isolated CDR region, an F(ab')2 fragment or a scFv fragment, and wherein the region

- (a) consists of the sequence as set forth in one of the designated Seq ID NOs.;
- (b) differs from the sequence of a designated SEQ ID NO. due to degeneracy of the genetic code but encodes the same amino acids; or
- (c) differs from the sequence of a designated SEQ ID NO. as a result of an allelic variation.

151. (withdrawn) A biologically functional vector system comprising a polynucleotide according to claim 150 which is capable of introducing the polynucleotide into the genome of a host organism.

152.(withdrawn) A host cell transformed with a polynucleotide according to claim 150.

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

- (a) isolating lymphocytes from a subject having TSH receptor antibody activity greater than 0.04 units of International Standard NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor,
- (b) immortalizing the isolated lymphocytes, and
- (c) cloning the immortalized lymphocytes to produce an immortalized colony secreting a human monoclonal antibody reactive with the TSH receptor.

157. (withdrawn) The process of claim 156, wherein the subject has TSH receptor antibody activity greater than 0.1 units of International Standard NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor.

158. (withdrawn) The process of claim 157, wherein the subject has TSH receptor antibody activity greater than 0.2 units of International Standard NIBSC 90/672 per mL of serum with

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

162. (withdrawn) A process for making a human monoclonal antibody reactive with TSH

receptor comprising the steps of:

(a) isolating lymphocytes from a subject having TSH receptor antibody activity greater than 0.1 units of International Standard NIBSC 90/672 per mL of serum with respect to stimulation of

cAMP production by cells expressing the TSH receptor;

(b) immortalizing the isolated lymphocytes, and

(c) cloning the immortalized lymphocytes to produce an immortalized colony secreting a human monoclonal antibody reactive with the TSH receptor.

163. (withdrawn) The process of claim 162, wherein the subject has TSH receptor antibody

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

167. (withdrawn) The process of claim 162, wherein the isolated lymphocytes are immortalized by infection with Epstein Barr virus, and the thus immortalized lymphocytes are fused with a mouse or human cell line to form the immortalized colony.

168. (withdrawn) A method for screening for autoantibodies to TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from an autoimmune disease with an immune reaction to the TSH receptor, said method comprising the steps of:

(a) obtaining a sample of body fluid from said subject;

(b) providing a pair of binding molecules, said pair comprising a first molecule comprising a binding partner according to claim 121, or a further binding partner according to claim 138, and a

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

169. (withdrawn) The method of claim 168, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable.

170. (withdrawn) The method of claim 168, wherein the first molecule has an affinity for the TSH receptor of  $10^{10}$  molar<sup>-1</sup> or greater.

171. (withdrawn) The method according to claim 168, wherein the second molecule comprises full length TSH receptor, or one or more epitopes thereof or a polypeptide comprising one or more epitopes of a TSH receptor.

172. (withdrawn) A method for screening for autoantibodies to TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

(c) contacting said sample with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) said polyclonal antibody; and

(d) monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

173. (withdrawn) A method for assaying for TSH or related ligands comprising the steps of

(a) obtaining a sample to be assayed for TSH or related ligands;

(b) providing a pair of binding molecules, said pair comprising a first molecule comprising a

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

- (a) providing a pair of binding molecules, said pair comprising a first molecule comprising a binding partner according to claim 121, or a further binding partner according to claim 138, and a second molecule comprising a binding region with which the first molecule interacts;
- (b) contacting the potential binding partner to be evaluated with said first molecule and said second molecule so as to permit the second molecule to interact with either the potential binding partner to be evaluated or the first molecule; and
- (c) monitoring the interaction of the second molecule with the potential binding partner to be evaluated, wherein competition with the binding of the first molecule to the second molecule indicates that the potential binding partner being evaluated binds to the TSH receptor.

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

178. (withdrawn) The anti-idiotypic antibody of claim 177, which is 7E51 IgG.

179. (withdrawn) A method for treating autoimmune disease associated with an immune reaction to the TSH receptor in a subject, comprising administering to the subject a therapeutically effective amount of a binding partner according to claim 121, or a further binding partner according to claim 138.

180. (withdrawn) The method of claim 179, wherein the binding partner stimulates the TSH receptor.

181. (withdrawn) The method of claim 179, wherein the binding partner or further binding partner interacts with the TSH receptor to inactivate it or render it unresponsive to TSH, TSH receptor autoantibodies or other stimulators.

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

185. (withdrawn) The method of claim 184, further comprising the step of administering an additional agent, different from the binding partner, capable of stimulating the TSH receptor.

186. (withdrawn) The method of claim 185, wherein the additional agent is selected from the group consisting of recombinant human TSH and bioactive variants, analogs, derivatives and fragments thereof.

187. (withdrawn) A method of treating autoimmune disease associated with an immune reaction to the TSH receptor in a subject, comprising administering to said subject a therapeutically effective amount of an anti-idiotypic antibody according to claim 177 or 178, whereby administration of said anti-idiotypic antibody substantially inhibits interaction of the TSH receptor with autoantibodies present in the patient's circulation, wherein said interaction of said autoantibodies and said TSH receptor is responsible for, or is associated with, said

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

wherein the binding partner has a characteristic of patient serum TSH receptor autoantibodies and according to claim 121 that stimulates the TSH receptor, and an agent different from the binding partner capable of stimulating TSH receptors for simultaneous or sequential use in stimulating tissue containing the TSH receptor.

190. (previously presented) The combination of claim 189, wherein the agent is selected from the group consisting of recombinant human TSH and bioactive variants, analogs, derivatives and fragments thereof.

191. (previously presented) The combination of claim 189, wherein the agent acts independently of binding to the TSH receptor.

192. (withdrawn) In combination, a binding partner according to claim 121, or a further

Appln No.: 10/537,280

Amendment Dated: October 22, 2007

Reply to Office Action of August 22, 2007

195. (withdrawn) A process of preparing a preparation required to comprise a defined concentration of TSH receptor antibody or antibodies, which process comprises providing a binding partner according to claim 121, or a further binding partner according to claim 138, as a suitable preparation having the required defined concentration of TSH receptor antibody or antibodies.

196. (withdrawn) A process for preparing a human recombinant antibody or a fragment thereof comprising cloning a human monoclonal antibody to the TSH receptor or a fragment derived therefrom that binds to TSH receptor, and expressing the cloned antibody or fragment.